Where can we use real-world evidence?

When Are Phase III Trials Viable/Not Viable?

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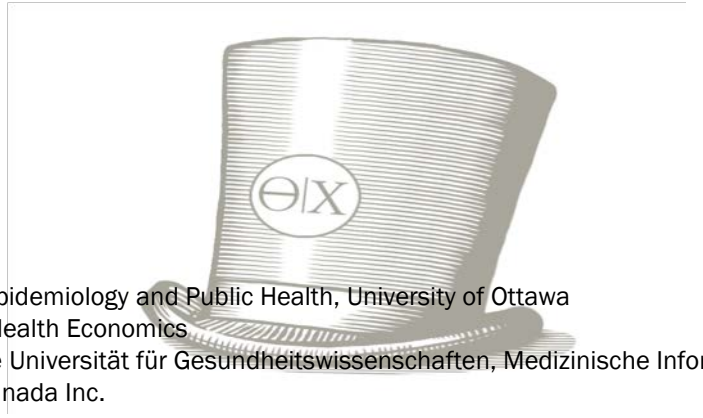


CAPT Conference 2019: Driving Health Innovation: Harnessing the Power and Value of Real-World Evidence"
October 22, 2019. MaRS Discovery District, Toronto.)

Disclosures

- I have worked for public and private sector organizations that might be interested in what I have to say.

Public / not-for-profit

Ontario CED member 2015-2019 • PMPRB Advisor / Working Group member • CADTH (pCODR EGP 2015-present, pERC committee member 2015-2017, Strategic advisor (early scientific advice / real-world evidence), CDR)• PAAB consultant (code changes) • Health Canada Strategic Policy Branch • Federal Innovation Council • Genome Canada • CD Howe Institute • ISPOR • IHE HTAi • CPhA • CHEO Research Institute

Private / for-profit

AbbVie • Amgen • AstraZeneca • Boehringer Ingelheim (Canada) Ltd. • Bristol Meyers Squibb • Celgene • CSL Behring • Gloval and Canadian onsultancies (Cornerstone, Evidera, IQVIA, Pivina etc.) • Danish Life Sciences Council • Eli Lilly • Esai • GSK • Janssen • Leo Pharma • Lundbeck • Merck • Novo Nordisk • Otsuka • Pfizer • Purdue • Taiho • Takeda • Legal firms (as expert witness)

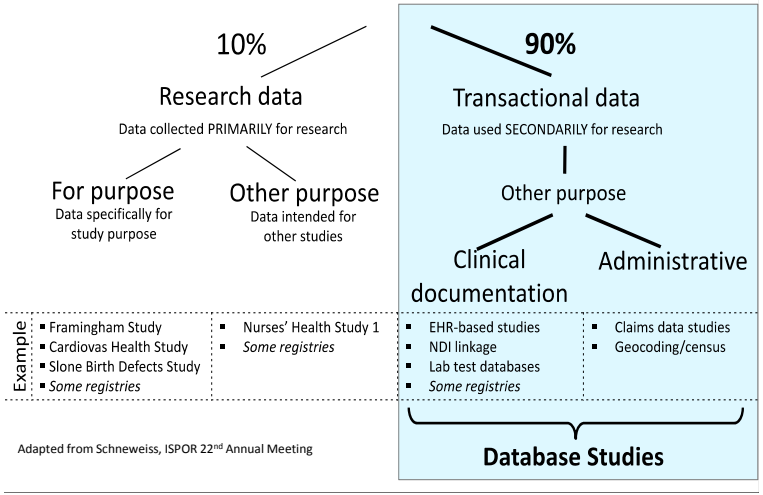
Overview of what I am going to address…

- What do we mean by RWE, observational data, phase 2*, and phase 3 data?
- What is the value of a positive phase 2 trial?
  - What is the chance of receiving a positive pERC recommendation?
  - What is the chance they are wrong?
  - What are the implications of misleading results?
  - What are the implications of overestimating benefit?
- Is a phase 3 trial always viable?

*Arabic numerals used to avoid false positives.

RWD, observational data and phase 2 study

"potential for complementing the knowledge gained from traditional clinical trials, whose well-known limitations make it difficult to generalize findings to larger, more inclusive populations of patients, providers, and health care delivery systems or settings that reflect actual use in practice."[1]



TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE

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"highly controlled"

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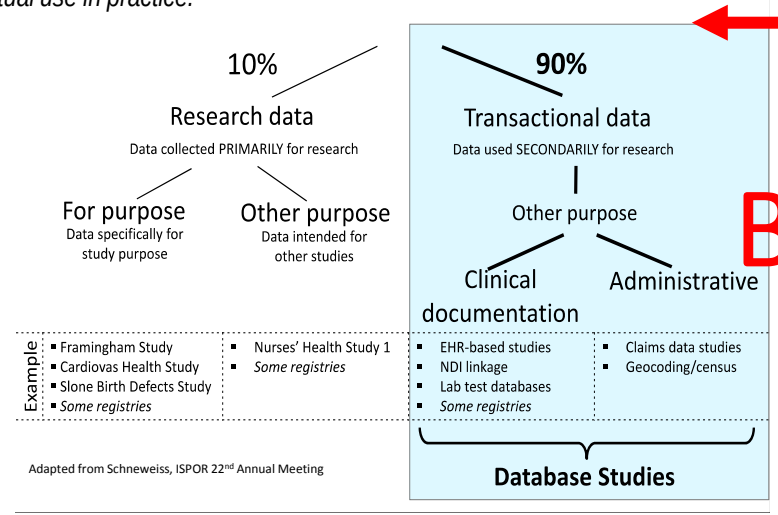

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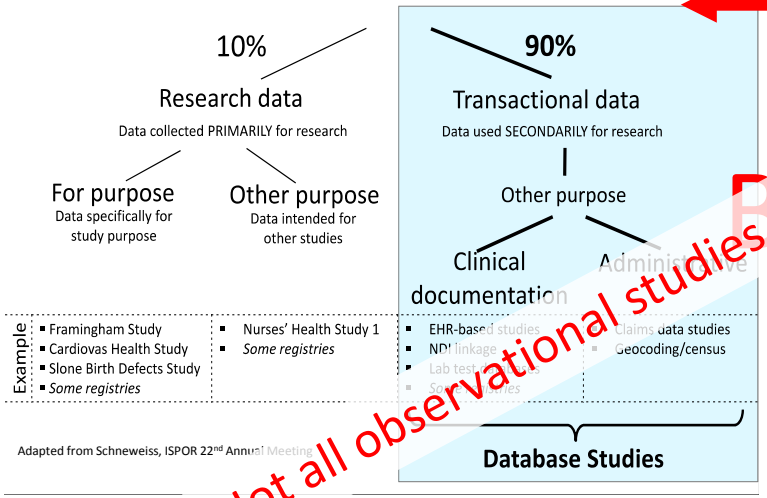

Adapted from Schneweiss, ISPOR 22nd Annual Meeting

Not all observational studies are real world studies

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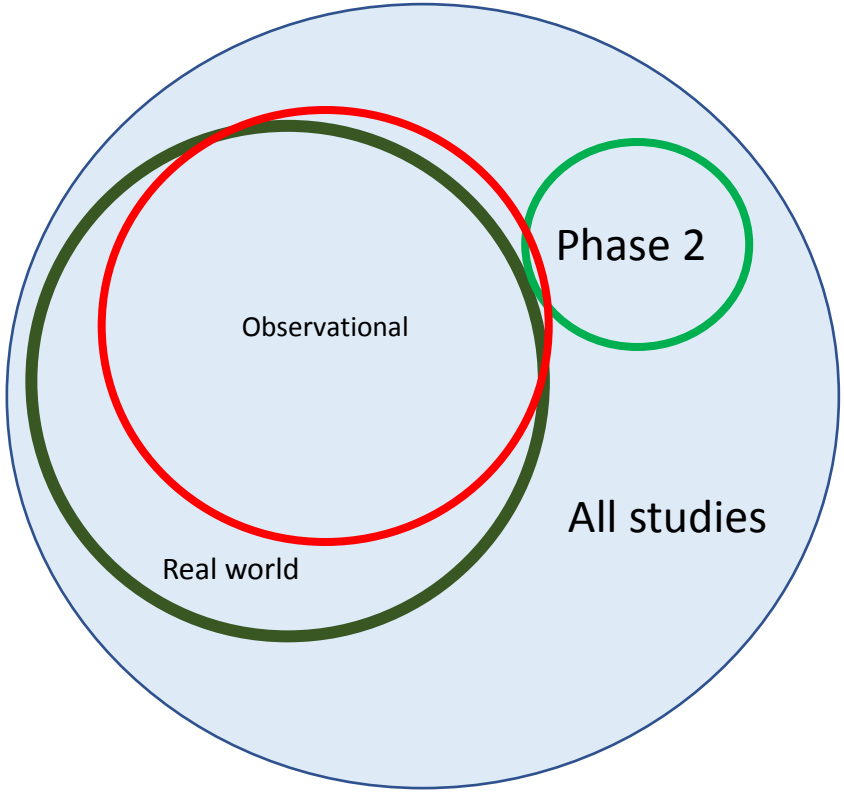

RWE Venn

What is the value of phase 2 data?

- What is the chance of receiving a positive pERC recommendation?
  - Until April of this year, pERC positive recommendations were issued for **phase 2** data **56% of the time**, while **phase 3/4** data led to **81% positive recommendations***
  - Therefore, chance of positive recommendation is 30 % lower (95% CI 4-49%) with phase 2 data.
  - Non-oncology recommendations, in contrast, are often positive with non-comparative or phase 2 data (e.g., sofosbuvir + ribavirin, asfotase alfa, nitisinone)

*Personal communication, Fergal Mills , Innomar pCODR Tracker®

What is the chance pERC is wrong?

- Current success rate for phase 2 applications to pERC is 56%.[1]
- Presumably a positive phase 2 leads to a phase 3
- In contrast the probability of success of a phase 3 drugs is ~35% in oncology for all indications and ~49% for "lead" indications.
- Therefore, pERC may be optimistic. They are more positive (56% vs. 49%) then the overall picture for oncology.

1. Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. *Biostatistics*. 2019;20(2):273-286. doi:10.1093/biostatistics/kxx069

On the other hand…

Drugs with negative recommendations based on non-comparative, phase 2 data

Drug	Year	Comment on phase 3?	Phase 3 trial	Outcome
Alectinib (Alencensa)	2017	Yes	ALUR	Positive
Brigatinib (Alunrig)	2019	No	ALTA-1L	Positive
Ofatumumab (Arzerra)	2015	Yes	COMPLEMENT-1	Positive
Blinatumomab (Blincyto)	2016	Yes	COG AALL1331 / 20120215	Positive
Daratumumab (Darzalex)	2016	Yes	MAIA	Positive
Ibrutinib (Imbruvica)	2016	Yes	iNNOVATE	Positive
Dabrafenib+Trametinib (Tafinlar+Mekinist)	2017	Yes	?	NA
Venetoclax (Venclexta)	2016	Yes	NCT02756897	Positive
Ceritinib (Zykadia)	2015	No	ASCEND-5	Positive

And yet on the *other* hand…..

Drugs with negative recommendations based on (positive) non-comparative, phase 2 data where phase 3 used very similar patient populations / regimens of original phase 2 study

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Ceritinib (Zykadia)	2015	No	ASCEND-5	Positive

What are the implications of misleading results?

- If pERC says no and is “wrong”, lost opportunity for patients
  - This value would equal the value of treatment under conditions of value-based price negotiation
    - e.g., 1000 patients x 0.5 QALYs= 500 QALYS
  - Few phase 3 trials replicate phase 2 condition

What are the implications of misleading results?

- If pERC says yes and it wrong, then use of drug represents an opportunity cost on other patients.
  - The value of this would equal the value of treatment under conditions of value-based price negotiation.
  - Lost additional value through price premiums
    - e.g., 500 QALYs that are worth 600 healthcare system QALYs due to 20% price premium over generic.
  - So if there is a 50% chance of being wrong, saying “no” represents less loss to the health system.
    - Gain of 600 QALYs – 500 QALYs = 100 QALYs!

Is a phase 3 trial always feasible?

- Yes, but it is not always desirable.

Final thoughts

- We can’t predict which phase 3 trials will fail
  - But we know a proportion of them will
- We know effect sizes will go down on average
  - But we don’t know by how much
- Erring on the side of “no” will create gains for health system value.
  - But identifiable patients will be aware of the loss.

Those who have knowledge, don't predict.
Those who predict, don't have knowledge.

--Lao Tzu, 6th Century BC Chinese Poet

Don Husereau

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Where RWE can be used to support suboptimal evidence across all clinical development phases.

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CADTH
RWE Lead, Manager – Program Development

CAPT Conference
October 22nd, 2019

CADTH Evidence Driven.

What is Real-World Evidence (RWE)?

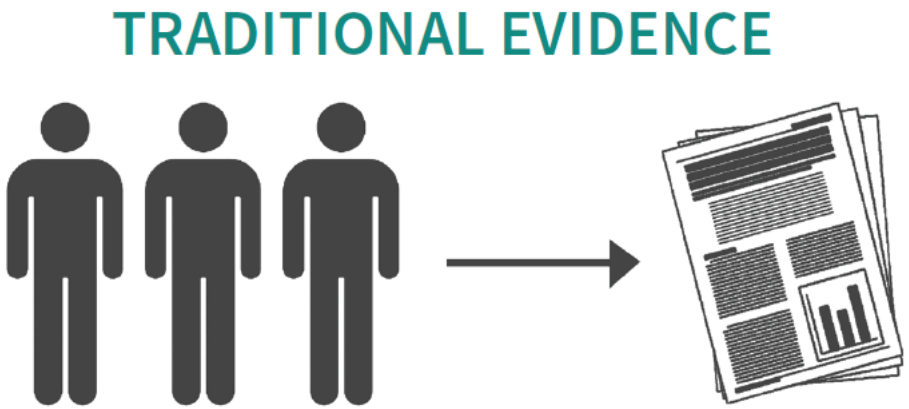
CADTH

What is RWE?

RWD is an overarching term for data that are not collected in the context of conventional randomised controlled trials (RCTs).

Real-world evidence (RWE) is the evidence derived from the analysis and/or synthesis of **real-world data (RWD)**.

What is RWE?



- Randomized controlled trials (RCTs) have been the gold standard
- Patients are quite homogenous
- Data collected is closely controlled and monitored
- High internal validity, Low external validity

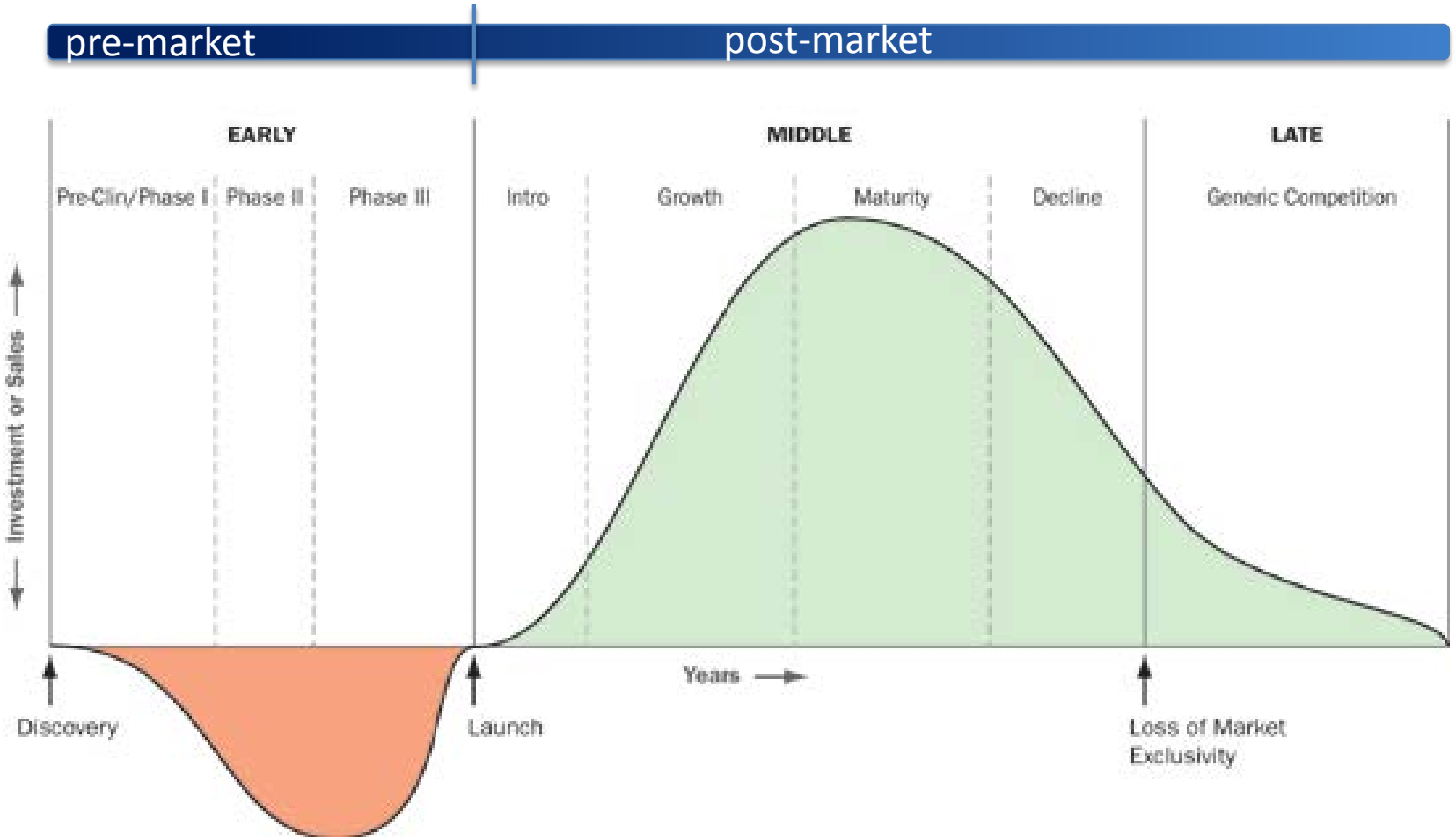
* adapted from www.nehi.net

What is RWE?

- Data comes from various non-RCT sources
- Patients are quite heterogenous
- Data collected is real-world practice settings
- Low internal validity, High external validity

* adapted from www.nehi.net

Drug Product Lifecyle



* adapted from pharmaexec.com

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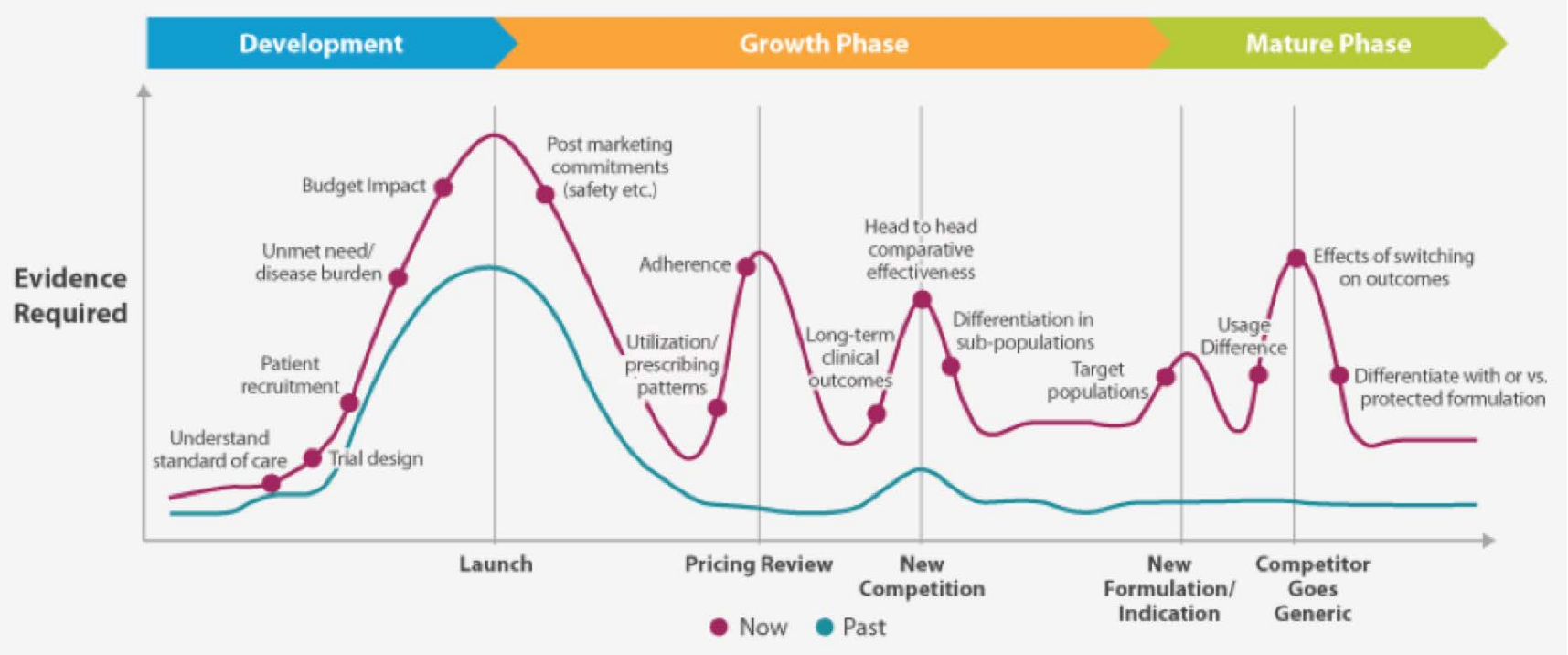
Drug Product Lifecyle



* adapted from McKinsey Practice Perspectives on RWD.

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Regulatory Position on RWE

International guidance on regulatory use of RWE includes:

- FDA Sentinel initiative (May 2008, Feb 2016)
  - safety of FDA-regulated medical products
- FDA RWE Framework (Dec. 2018)
  - monitor postmarket safety and adverse events and to make ***regulatory decisions***

Regulatory Position on RWE

International guidance on regulatory use of RWE includes:

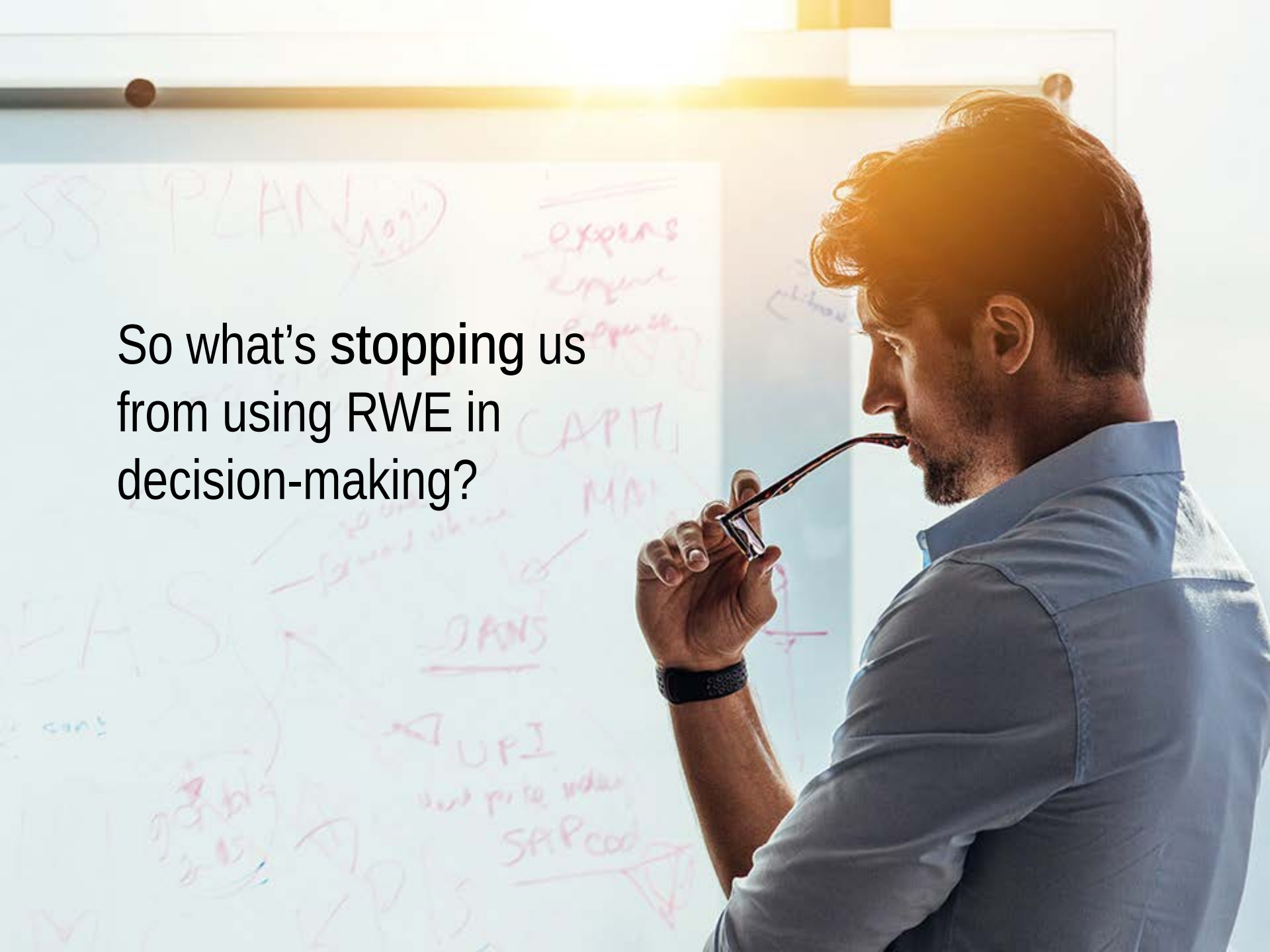
- National Institutes of Health (NIH) Collaboratory
- National Patient-Centered Clinical Research Network (PCORnet)
- In 2013, EMA issued guidelines for RWE studies, requiring risk-benefit data in addition to post-authorization safety studies.

Regulatory Position on RWE

Health Canada guidance on regulatory use of RWE includes:

- Guidance documents on RWD - overarching principles to guide the generation of RWE that would be consistent with the regulatory standard

- Notice to Industry on Submissions with RWE:
  - encourage RWE submissions
    - for populations often excluded from clinical trials (ex: children, seniors, and pregnant women);
    - where clinical trials are unfeasible
    - where clinical trials are unethical


So what's stopping us from using RWE in decision-making?

Factors to consider

Barriers to use of RWD/E by HTA and Payers:

- managing uncertainty
  - RCT vs. RWE
  - regulatory/decision grade
  - acceptable levels of uncertainty
- illustrating unmet need
- lack of consensus on guidelines or principles
- trustworthiness / transparency
- lack of knowledge and skill

Ongoing activities

Partnership between HTA and Regulator

- collaboration between CADTH, HC and INESSS
- produce strategy for use of RWE across the product lifecycle *(fall 2019)*
- guidance documents for use of RWE for drugs:
  - *principles and expectations of RWD*
  - *appropriate approaches for RWE*

Ongoing activities

Formation of RWE Drug Core Action Team (CAT)

- collaboration between HTA and regulator
- contribution from payers, data holders/producers, academics, and industry
- strategic-thinking and address common barriers
- improved transparency and awareness

Ongoing activities

Involvement in CanREValue Collaboration:

- multi-year grant led by Dr. Kelvin Chan

Goal:

  - develop a framework for Canadian provinces to generate and use RWE for cancer drug funding decisions

Ongoing activities

Potential Impact:

- **reassessment** of cancer drugs by recommendation-makers
- **refinement** of funding decisions or
- re-negotiations/re-investment

Ongoing activities

ISPOR RWE Transparency Initiative

- multi-stakeholder participation including HTA
- identify practical implementation steps to facilitate routine registration of RWE studies
- includes posting of protocol, with date-stamp
- white paper currently available

Next steps

- continued collaboration between stakeholders to provide guidance and framework
- continued collaboration with industry and data stewards to produce “appropriate” RWD
- improve capacity and skill across HTA and payers
- “dive-in” with pilots

CADTH Evidence Driven.

ACMTS Preuves à l'appui.